

### **REMARKS**

Claims 1-20 are currently pending in this application.

Applicants have amended the specification on page 6 to correct a misspelling of the word “polyoxyethylene.”

In order to clarify the scope of the claims and/or to correct typographical errors, applicants have amended claims 1, 2, 5-10 and 13-14. For example, applicants have amended claim 1 to recite “an inorganic or organic acid, wherein the acid has a concentration in a range that corresponds to a pH range of 2.5 - 4.5 in aqueous solution.” Support for this amendment is found in the specification, e.g., on page 3, lines 30-33. Furthermore, applicants have amended claims 2, 7, 9 and 13-14 to recite “% w/w.” Support for this amendment is found throughout the specification, e.g., in the specification on pages 8-9, Formulation Examples. Claims 5 and 6 have been amended to further recite particular inorganic or organic acids. Applicants have also amended claim 8 to correct the spelling of polyoxyethylene and claim 10 to provide the proper antecedent basis.

Applicants make these amendments without prejudice and without waiver of applicants’ right to pursue the originally-filed subject matter in a continuing application claiming priority herefrom under 35 U.S.C. § 120.

No new matter is being presented by these amendments.

#### **A. Objections**

The Examiner has objected to the misspelling of the word “polyoxyethylene” in the specification on page 6, line 16 and in claim 8. Applicants have amended the specification and claim 8 to correct this typographical error.

#### **B. Rejections under 35 U.S.C. § 112, second paragraph**

Claims 1-20 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Specifically, the Examiner asserts that the recitation “inorganic and organic acids having a pH range of 2.5-4.5 in aqueous solution” in claim 1 is confusing “because the pH of a solution is determined by the amount of acid present ....” The Examiner also asserts that the

recitation of “an acid selected from the group consisting of one or more of inorganic and organic acids...” may be interpreted in different ways. Applicants have amended claim 1 to recite “an inorganic or organic acid, wherein the acid has a concentration in a range that corresponds to a pH range of 2.5 - 4.5 in aqueous solution,” thus clarifying the scope of the claim and rendering moot the Examiner’s rejection.

Claims 2, 7, 9, 13 and 14 stand rejected for reciting ranges of amounts of components based on weight, wherein the Examiner asserts that the referred weight term is unclear, i.e. weight of total formulation, weight of a component relative to other components, or the weight of a component prior to the addition of propellant. Applicants have amended these claims to recite the term “% (w/w)” instead of “weight.” This should clarify that the weight percent refers to mass of component divided by the total mass of the total formulation. Thus, applicants have rendered moot the Examiner’s rejection.

Claim 10 stands rejected because the term “anhydrous crystalline form of tiotropium bromide” has insufficient antecedent basis. Applicants have amended claim 10 to correct this inadvertent error, thus rendering moot the Examiner’s rejection.

The remaining claims stand rejected as being dependent on a rejected claim. Based on the foregoing amendments and remarks, dependent claims 3-6, 8, 11-12 and 15-20 should no longer be indefinite.

### **C. Rejections under 35 U.S.C. § 102**

Claims 1-4, 6, 8-9 and 15 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Keller et al. (WO 00/07567), where Keller et al., (U.S. Patent No. 6,475,467, hereinafter “Keller”) is being used as the English language equivalent of WO 00/07567. Specifically, the Examiner asserts that Keller discloses throughout the specification tiotropium and tiotropium bromide, liquid propellants, including hydrofluorocarbons, cosolvents, surface-active agents and a device to administer aerosol compositions. The Examiner, however, acknowledges that Keller does not include inorganic and organic acids in the Examples but instead, asserts that Keller discloses citric acid or ascorbic acid as potential buffering compounds in the aerosol formulations. The Examiner further acknowledges that Keller does not explicitly teach citric acid and ascorbic acid as organic acids but that this would have been readily apparent to any person of ordinary skill in the art. Applicants traverse.

The standard for anticipation is set forth in MPEP 2131 – “a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently

described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Applicants have amended claim 1 to recite the element of inorganic or organic acid as having a concentration in a range that corresponds to a pH range of 2.5 - 4.5 in aqueous solution. The pH now reflects the amount of inorganic or organic acid used in the composition. Keller fails to disclose a composition comprising, *inter alia*, an inorganic or organic acid having a concentration corresponding to the pH range of 2.5 – 4.5, and therefore Keller does not anticipate amended claim 1 or claims 2-4, 6, 8-9 and 15, which depend either directly or indirectly from claim 1. Applicants respectfully request withdrawal of this rejection.

Claims 1-9, 11, 15 and 20 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Jager et al. (U.S. Patent No. 6,045,778, hereinafter “Jager”). The Examiner asserts that Jager discloses aerosol solution formulations (and devices) comprising medicaments, an HFC propellant, a cosolvent and an acid and subsequently describes these components either by name or concentration according to the Examiner’s reading of Jager. Applicants traverse.

The Tables in Jager describe either ipratropium bromide or fenoterol hydrobromide aerosol solution formulations. For example, Table 1 and col. 6 (lines 17-19), which the Examiner refers to in his arguments, are directed to specific conditions for ipratropium bromide solution formulations. According to Jager (e.g., col. 6, lines 12-17, 38-41, 43-51, 61-66), stability, solubility, concentrations of components, etc. will depend primarily on the chemical composition of the formulation.

The presently claimed invention is different from Jager in that it is directed to a specific composition having a specific medicament – tiotropium bromide or a pharmaceutically acceptable salt or hydrate thereof. Although Jager generally discusses tiotropium bromide as a possible medicament (see col. 4, lines 17-22 and claims 1 and 4-6), it does not provide the detailed teachings of the tiotropium HFC formulations of the claimed invention. For example, the tiotropium composition recited in amended claim 1 comprises a narrow concentration of inorganic or organic acid corresponding to a pH range of 2.5-4.5, which is not taught expressly or inherently in Jager. Moreover, the concentrations of tiotropium bromide, water and solvent are selective to the stable pharmaceutical solution formulations of the present invention and again are not taught expressly or inherently in Jager. For these reasons, Jager does not anticipate amended claim 1 or claims 2-9, 11, 15 and

20, which depend either directly or indirectly from claim 1. Applicants respectfully request withdrawal of this rejection.

**D. Rejections under 35 U.S.C. § 103**

Claims 13, 17 and 19 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Jager. The Examiner acknowledges that “Jager does not explicitly teach an aerosol formulation comprising tiotropium bromide monohydrate, a device containing an aerosol formulation comprising tiotropium bromide monohydrate, nor a device in the form of a MDS comprising the composition of claim 1.” Applicants traverse.

Applicants have amended claim 1, with claims 13, 17 and 19 being indirectly dependent therefrom. Amended claim 1 recites a composition comprising tiotropium bromide or pharmaceutically acceptable salt or hydrate thereof, an HFC propellant, a solvent and an inorganic or organic acid, wherein the acid has a concentration in a range that corresponds to a pH range of 2.5 - 4.5 in aqueous solution.

Jager neither teaches nor suggests the specific acid concentration range of the tiotropium composition in amended claim 1 or the other specific claim limitations found in claims 13, 17 and 19. For example, Table 1 of Jager teaches ipratropium bromide solution formulations containing ipratropium bromide (0.001-2.5% w/w), ethanol (1-50% w/w), HFC (50-99% w/w), inorganic acid (0.01-0.00002 normal, corresponding to pH range of 2.0-4.7) and water (0-5.0%). In claim 13 of the present invention, the composition comprises tiotropium bromide monohydrate (0.0001-0.5% w/w), ethanol (5-50% w/w), water up to 5% w/w, an acid in an amount to yield a pH range of 2.5-4.5 in aqueous solution and an HFC propellant. At a minimum, Jager does not teach or suggest all the elements of the rejected claims, and thus, one of the three basic criteria needed to establish a *prima facie* case of obviousness – (1) suggestion or motivation to modify the reference(s) or to combine reference teachings, (2) reasonable expectation of success and (3) prior art reference, or references when combined, must teach or suggest all the claim limitations – is not met. MPEP 2142. For this reason, the teaching of Jager does not make the present claims obvious.

Applicants respectfully request that the Examiner withdraw this rejection.

Claims 10, 12, 14, 16 and 18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Jager, as applied to claims 13, 17, and 19, and further in view of Pairet et al. (US 2002/0122773, hereinafter “Pairet”). The Examiner acknowledges that Jager lacks

the teaching of a composition comprising anhydrous crystalline tiotropium bromide, the composition being free of water, and the composition contained in a device for administration of aerosol compositions. The Examiner further asserts that Pairt cures this defect by disclosing crystalline tiotropium bromide *monohydrate*, arguing that one of skill in the art would know to use the *anhydrate* based on Pairt's teachings. Applicants traverse.

As discussed above, Jager by itself is insufficient to meet the criteria necessary for a *prima facie* case of obviousness. Pairt does not cure this defect by disclosing crystalline tiotropium bromide monohydrate, which is a different crystalline form from that found in claim 10.

Applicants respectfully request that the Examiner withdraw rejection of claims 10, 12, 14, 16 and 18.

Claims 1-5, 7-9, 15 and 20 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hassan et al. (WO 00/47200, hereinafter "Hassan") in view of Lewis et al. (~~US 2002/0183293~~ US 2002/0025299, hereinafter "Lewis"). Applicants traverse.

As an initial matter, the inventors of U.S. Application No. 2002/0183293 are "Banerjee et al." and not "Lewis et al.," as described by the Examiner. Moreover, the subject matter of Lewis cited and discussed by the Examiner in the Office Action does not correspond with the subject matter of U.S. Application No. 2002/0183293. As such, applicants believe the Examiner meant to cite U.S. Application No. 2002/0025299 A1 as corresponding to Lewis. If this is incorrect, applicants kindly request clarification as to which Lewis US patent application forms the basis of the Examiner's rejection.

Hassan discloses "(A) and (B) separately or in admixture in a solution or dispersion in a propellant or a nebulizable composition comprising a dispersion of the active ingredient in an aqueous, organic or aqueous/organic medium [emphasis added]." Here, Hassan teaches (1) a solution or dispersion of two actives in propellant or (2) a dispersion of active in aqueous and/or organic medium. Hassan further discloses that both actives can be in salt form. Unlike Hassan, the present invention relates to a solution of one active in propellant, solvent and acid. Moreover, amended claim 1 recites a composition wherein the inorganic or organic acid has a concentration in a range that corresponds to a pH range of 2.5 - 4.5 in aqueous solution. Hassan neither teaches nor suggests that its actives are in solution with an acid having the concentration as recited in amended claim 1.

Lewis discloses an aerosol solution composition comprising an active (mainly formoterol), a propellant, cosolvent, optionally a low volatility component, and a small amount of mineral acid. Furthermore, Lewis' disclosure in paragraphs 0020 and 0054 are directed to the *apparent* pH of the *solution*. In contrast, amended claim 1 of the present invention recites a composition wherein the inorganic or organic acid component has a concentration in a range that corresponds to a pH range of 2.5 - 4.5 in aqueous solution. Lewis neither teaches nor suggests that its mineral acid has the concentration as recited in amended claim 1, but instead Lewis discloses that the mineral acid is used to adjust the pH of the solution (see paragraph 0054).

Because both Hassan and Lewis lack the teaching or suggestion of the acid limitation of base claim 1, the combination of Hassan and Lewis does not obviate the subject matter of the claimed invention. Applicants respectfully requests that the Examiner withdrawal this rejection.

#### **E. Double Patenting**

The following claims stand provisionally rejected on the grounds of nonstatutory double patenting:

(1) Claims 1-6 and 8 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-6 of co-pending Application No. 10/392,559;

(2) Claims 1-6, 8, 9 and 10 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-6 of co-pending Application No. 10/400,127;

(3) Claims 1 and 10 are provisionally rejected on the ground of nonstatutory double patenting over claims 1, 2 and 8 of co-pending Application No. 10/976,624 in view of Lewis;

(4) Claims 1-3, 15 and 20 are provisionally rejected on the ground of nonstatutory double patenting over claims 9, 22-24, 27 and 29 of co-pending Application No. 10/976,688 in view of Lewis;

(5) Claims 1-3, 15 and 20 are provisionally rejected on the ground of nonstatutory double patenting over claims 12, 21-23, 26 and 28 of co-pending Application No. 10/977,753 in view of Lewis; and

(6) Claims 1-8 and 15 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-19 and 24 of co-pending Application No. 11/169,876.

In response, applicants note that none of the claims of the above-identified co-pending applications have been issued or allowed, and applicants will address any such obviousness issue by argument, amendment, or terminal disclaimer when the Examiner indicates that the instant application contains allowable subject matter and the Examiner maintains the rejection.

**F. Other Matter**

The Examiner has suggested that applicants write out the word hydrofluorocarbon followed by its abbreviation in parentheses in claim 1. Applicants have adopted the Examiner's suggestion in claim 1.

**G. Conclusion**

In view of the above amendments and remarks, applicants respectfully request that Examiner pass this application to issuance.

If any points remain at issue which can best be resolved by way of a telephonic or personal interview, the Examiner is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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